

nodes decreased in size and became impalpable. After discharge in February 1989, he was treated with maintenance chemotherapy every 3 months for 2½ years. In October 1992, he had lt-inguin lymph-node swelling and lymphocytosis. His leukocyte count was 10,000/μl (neutrophils 23%, lymphocytes 72%), hemoglobin level of 10.2 g/dl, and platelet count of $9.2 \times 10^4/\mu\text{l}$. The peripheral blood and bone marrow were infiltrated by small to medium-sized lymphoid cells. Immunophenotypic analysis of the lymphoid cells showed a preponderance of CD5(+), CD19(+), CD20(+), and surface Ig(-) cells. In contrast, lt-cervical lymph-node biopsy showed NHL (diffuse, mixed-cell type). He was admitted to hospital and treated with remission-induction chemotherapy (cytosine arabinoside, aclarubicin, and methyl prednisolone). Lt-inguin lymph-node swelling disappeared, but lymphocytosis continued. In May 1994, his leukocyte count increased to 17,100/μl (neutrophils 20%, lymphocytes 73%), and low-dose etoposide (25 mg/day) as started. This was continued intermittently until October 1995, when swelling of the lt-inguin lymph node and interstitial pneumonia developed. Lt-inguin lymph-node biopsy revealed the proliferation of small lymphoid cells, which were compatible with the pathological features of CLL. The patient died of respiratory failure on November 29, 1995.

Sequential immunogenotypic analysis was performed on lymphoid cells obtained from the lymph node (October 1992), peripheral blood (August 1994), and bone marrow (December 1994). DNA from these materials showed identical rearrangements with a J_H gene probe (Fig. 1). Analysis with kappa, lambda, and TCR-β gene probes showed germline configuration.

In conclusion, the pathological and immunophenotypic analysis suggested that the patient had discordant lymphoma which consisted of CD5(-) NHL and CD5(+) CLL. The identical immunoglobulin gene rearrangement provided evidence for the evolution of two morphologically distinct neoplasms from the same clone.

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Thromboembolic complication of splenectomy in unstable hemoglobin disorders: Hb Olmsted, Hb Köln

To the Editor: We read with interest the article by Thuret et al. [1] in the February 1996 issue concerning "Priapism Following Splenectomy in an Unstable Hemoglobin: Hemoglobin Olmsted . . ."

We share the authors' view that severe thromboembolic complications may follow splenectomy in patients who have severe chronic hemolytic disease, particularly in those cases that remain severely anemic following

splenectomy. However, their statement that the original case of hemoglobin Olmsted hemolytic anemia died at age 37 of pulmonary infarction is not correct. The authors appear to have confused our case of hemoglobin Olmsted disease with the case of fatal pulmonary infarction in a patient with hemoglobin Köln disease who had been splenectomized, reported by Egan and Fairbanks [2]. We concur with the authors' observation that the isopropanol test is negative for unstable hemoglobin in specimens containing hemoglobin Olmsted, but that commonly used heat tests for hemoglobin instability are strongly positive. In screening for unstable hemoglobins, both tests must be used.

This letter permits us the opportunity to provide the final note concerning the original case of hemoglobin Olmsted hemolytic anemia [3]. The patient continued to have severe hemolytic anemia, with venous blood hemoglobin concentration usually in the range of 60–80 g/l. Transfusions were required periodically. At age 36 he experienced acute severe hepatic and renal failure, with serum bilirubin concentration in excess of 30 mg/dl ($>500 \mu\text{mol/l}$), and he died. During this terminal interval, he also had a severe hemorrhagic diathesis that appeared to be due to disseminated intravascular coagulation. Whether this coagulopathy contributed to hepatic and renal failure is uncertain, as postmortem examination was declined by his family.

Apparently, both our case and the Marseille case of Thuret et al. represented de novo mutations. The case in Marseille may now be the only known surviving case of hemoglobin Olmsted hemolytic anemia.

As regards the effect of splenectomy in hemoglobin Köln disease, although we have advised against it, splenectomy has nonetheless been performed in about half the cases known in four Minnesota families with this disorder. We are unaware of any other cases that have manifested either erythrocytosis or thromboembolic complications following splenectomy. The anemia does not appear to be ameliorated, but it is usually very mild or completely compensated before splenectomy. Patients seem generally to be about as well after splenectomy as before.

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Type III Hypersensitivity Reaction With the Use of Interferon-α

To the Editor: Interferon-α (IFN-α), produced by recombinant DNA technology, is in clinical use for the treatment of hematologic malignancies such as chronic myelogenous leukemia (CML), as well as other malignant and nonmalignant conditions [1]. Side effects described with the use of IFN include a flu-like syndrome, as well as gastrointestinal, central nervous system, and hematologic toxicities. There is evidence that IFNs may enhance pre-existing autoimmune disorders or induce their occurrence [1]. This report describes a case of type III hypersensitivity, an uncommon side effect, in a patient with CML treated with IFN-α.

A 50-year-old woman was diagnosed with Philadelphia chromosome positive (Ph+) CML in June 1991. She was treated with IFN-α 2b (Intron

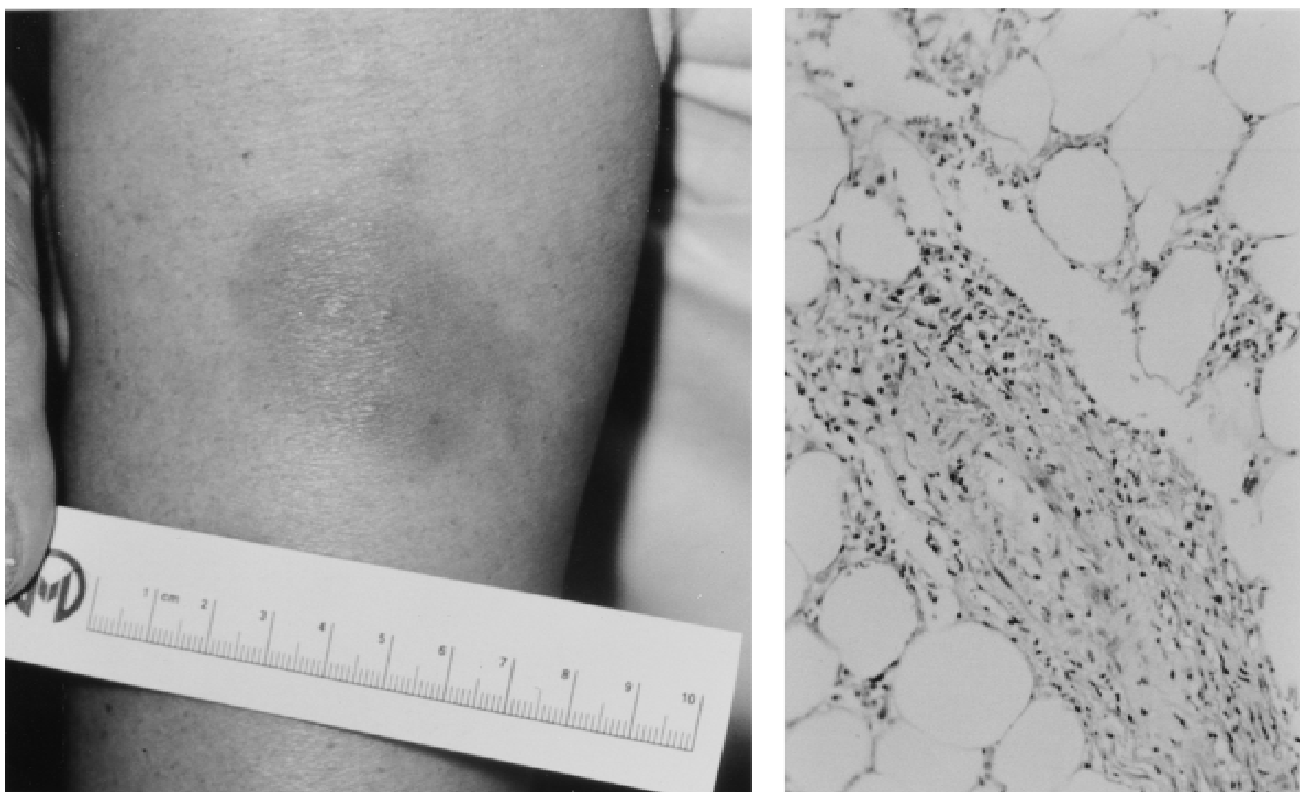


Fig. 1. Left: Appearance of one of the skin lesions at a site of INF injection (posterior aspect, right arm). Right: Photomicrograph (×400) of the skin biopsy specimen. See text for description.

A, Schering, NJ), 5,000,000 U/m²/day SC. An evaluation in February 1993 revealed a partial cytogenetic remission, with 55% of the analyzed cells showing a residual Ph⁺ chromosome. The patient achieved a complete cytogenetic and molecular remission (PCR for BCR-ABL was negative) after a course of high-dose cytosine arabinoside and idarubicin. In September 1994, re-emergence of Ph⁺ cells, along with clinical evidence of relapse, was documented. The patient was restarted on IFN- α 2b (Intron A) 3,000,000 U/day SC. Areas of skin erythema and subcutaneous induration appeared at each site of injection. The lesions measured 5–6 cm in diameter and developed several hours after IFN administration. Although the erythematous reactions decreased in severity as the injections continued, the formation of new indurated areas at the injection sites continued. Skin and subcutaneous biopsies were then obtained. Microscopic examination revealed a sparse superficial and deep perivascular interstitial infiltrate, composed of lymphocytes, histiocytes, plasma cells, neutrophils, and rare eosinophils beneath the normal epidermis. Flow cytometry demonstrated a heterogeneous population of T lymphocytes with a predominance of CD8, HLA-DR-positive (activated) T cells. Specific anti-INF antibodies were not measured. The patient was switched to IFN- α 2a (Roferon-A, Roche, Nutley, NJ) but demonstrated the same reactions observed with IFN- α 2b. After 2 weeks, IFN- α 2a was discontinued. The patient is currently being treated with hydroxyurea and remains in hematologic remission.

In a review of 524 patients with CML, treated with various types of IFN- α in six clinical trials, no skin reactions were reported other than exacerbation of psoriasis in two patients and skin dryness [2].

In our patient, the development of skin lesions upon re-introduction of IFN- α 2b along with the histological and flow cytometric findings are suggestive of a type III delayed hypersensitivity reaction. The production of antibodies to IFN has been well documented in the literature. These antibodies can neutralize IFN and may produce immune complexes that could lead to hypersensitivity reactions.

Several cases of cutaneous necrosis induced by the chronic administration of IFN have been described [3–5]. They include two patients with Kaposi's sarcoma and one case each of CML and multiple sclerosis treated with IFN- α or IFN- β . The skin biopsies performed in these patients reported findings compatible to those observed in our case, suggesting a similar pathophysiology.

The aim of this report is to alert health care workers to the potential occurrence of type III hypersensitivity to IFN- α . IFNs currently available for therapeutic use, despite being proteins of human origin synthesized by recombinant DNA technology, can be immunogenic and lead to this complication.

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